

**Cyclic Aliphatic Bromides Cluster (HBCD)**  
**(CASRN: 25637- 99- 4; 3194- 55- 6; 3194- 57- 8)**

**Systematic Review Supplemental File for the TSCA Risk  
Evaluation:  
Updates to the Data Quality Criteria  
for Epidemiological Studies**

EPA's Office of Pollution Prevention and Toxics (OPPT) developed data quality criteria for epidemiological studies. The first version of the criteria was documented in the [ [HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/application-systematic-review-tsca-risk-evaluations"](https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/application-systematic-review-tsca-risk-evaluations) ] document (EPA Document#740-P1-8001). The initial criteria were updated after considering EPA/OPPT's practical experience and comments from the public. This systematic review supplemental document describes the updated data quality criteria that EPA/OPPT intends to apply for the TSCA risk evaluations.

## Evaluation Criteria for Epidemiological Studies: General

Confidence Level (Score)	Description
<b>Domain 1. Study Participation</b>	
<b>Metric 1. Participant selection (selection, performance biases)</b>	
<b>Instructions:</b> To meet criteria for confidence ratings for metrics where 'AND' is included, studies must address both conditions. For metrics where 'OR' is included, studies must address at least one of the conditions stipulated.	
High (score = 1)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> All key elements of the study design are reported (e.g., setting, participation rate description, exclusion criteria, and methods of participant selection or case ascertainment) <b>AND</b> The reported information indicates that selection in or out of the study (or analysis sample) and participation in the study is likely representative of the exposure-outcome distribution of the participants for inclusion in the study.)</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> Some key elements of the study design were not present but available information indicates that selection in or out of the study (or analysis sample) and participation in the study is likely representative of the exposure-outcome distribution of the participants for inclusion in the study.)</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> Key elements of the study design and information on the population (e.g., setting, participation rate description, exclusion criteria, and methods of participant selection or case ascertainment) are not reported. <b>ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Von Elm&lt;/Author&gt;&lt;Year&gt;2008&lt;/Year&gt;&lt;RecNum&gt;111126&lt;/RecNum&gt;&lt;IDText&gt;4263036&lt;/IDText&gt;&lt;DisplayText&gt;2008&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111126&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="121521205718"&gt;111126&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;author&gt;Elm, E.&lt;/author&gt;&lt;author&gt;Altman, D. G.&lt;/author&gt;&lt;author&gt;Egger, M.&lt;/author&gt;&lt;author&gt;Pocock, S. J.&lt;/author&gt;&lt;author&gt;C.&lt;/author&gt;&lt;author&gt;Vandenbroucke, J. P.&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies&lt;/title&gt;&lt;secondary-title&gt;Epidemiology&lt;/secondary-title&gt;&lt;alt-title&gt;J Clin Epidemiol&lt;/alt-title&gt;&lt;short-title&gt;Journal of Clinical Epidemiology&lt;/short-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/full-title&gt;&lt;pages&gt;&lt;volume&gt;61&lt;/volume&gt;&lt;number&gt;4&lt;/number&gt;&lt;dates&gt;&lt;year&gt;2008&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 0950-2688&lt;/isbn&gt;&lt;label&gt;4263036&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;https://hero.epa.gov/heronet/index.cfm/reference/download/reference_id/4263036&lt;/url&gt;&lt;/related-urls&gt;&lt;/custom1&gt;&lt;electronic-resource-num&gt;10.1016/j.jclinepi.2007.11.008&lt;/electronic-resource-num&gt;&lt;/record&gt;&lt;/EndNote&gt;</b></li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> The reported information indicates that selection in or out of the study (or analysis sample) is significantly biased (i.e., the exposure-outcome distribution of the participants is likely not representative of the population of persons eligible for inclusion in the study.)</li> </ul>
Not rated/applicable	Do not select for this metric.
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 2. Attrition (missing data/attrition/exclusion, reporting biases)</b>	

Confidence Level (Score)	Description
<p>High (score = 1)</p>	<ul style="list-style-type: none"> <li>• <b><i>For cohort studies:</i></b> There was minimal subject loss to follow up during the study (or exclusion from the analysis) and outcome data were largely complete.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Any loss of subjects (i.e., incomplete outcome data) or missing exposure and outcome data were adequately* addressed (as described below), and reasons were documented when human subjects were removed from a study [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Missing data have been imputed using appropriate methods (e.g., multiple imputation methods), and characteristics of subjects with unavailable records are not significantly different from those of the study participants [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul> <ul style="list-style-type: none"> <li>• <b><i>For case-control studies and cross-sectional studies:</i></b> There was minimal subject withdrawal from the study (or exclusion from the analysis) and outcome data and exposure were largely complete.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Any exclusion of subjects from analyses was adequately* addressed (as described below), and reasons were documented when human subjects were removed from the study or excluded from analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul> <p><b>*NOTE for all study types:</b> Adequate handling of subject attrition can include: Use of imputation methods for missing data, and reasons for missing subjects unlikely to be related to outcome (for survival data, censoring was unlikely to introduce bias), and missing data were balanced in numbers across study groups, with similar reasons for missing data across groups.</p>
<p>Medium (score = 2)</p>	<ul style="list-style-type: none"> <li>• <b><i>For cohort studies:</i></b> There was moderate subject loss to follow up during the study (or exclusion from the analysis) and outcome data were nearly complete.</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Any loss or exclusion of subjects was adequately addressed (as described in the acceptable handling of subject attrition category) and reasons were documented when human subjects were removed from a study.</li> <li>• <b><i>For case-control studies and cross-sectional studies:</i></b> There was moderate subject withdrawal from the study (or exclusion from the analysis) but outcome and exposure data were largely complete</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Any exclusion of subjects from analyses was adequately addressed (as described above), and reasons were documented when human subjects were removed from the study or excluded from analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;]. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul>



Confidence Level (Score)	Description
Not rated/applicable	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 3. Comparison Group (selection, performance biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li><b><u>For ALL study types:</u></b> Any differences in baseline characteristics of groups were considered as potential confounders and were thereby controlled by statistical analysis (Source: OHAT). <b>OR</b></li> <li><b><u>For cohort and cross-sectional studies:</u></b> Key elements of the study design are reported (i.e., setting, inclusion and exclusion criteria, participant selection), and indicate that subjects were similar (e.g., recruited from the same eligible population and within the same time frame using the same inclusion and exclusion criteria, and were of similar age and sex). &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;U.S. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> <li><b><u>For case-control studies:</u></b> Key elements of the study design are reported indicate that that cases and controls were recruited from the same eligible population with the number of controls described, and eligibility criteria and are recruited with similar characteristics. &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;U.S. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> <li><b><u>For studies reporting Standardized Mortality Ratios (SMRs) or Standardized Incidence Ratios (SIRs):</u></b> Age, sex (if applicable) adjustment or stratification is described and choice of reference population (e.g., general population) is described.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><u>For cohort studies and cross-sectional studies:</u></b> There is only indirect evidence (e.g., stated by the authors without providing a description) that groups are similar (as described above for the high confidence rating).</li> <li><b><u>For case-control studies:</u></b> There is indirect evidence (i.e., stated by the authors without providing a description) that cases and controls are similar (as described above for the high confidence rating).</li> <li><b><u>For studies reporting SMRs or SIRs:</u></b> Age, sex (if applicable), and race (if applicable) adjustment or stratification is described in the text, but results tables are stratified by age and/or sex (i.e., indirect evidence); choice of reference population is described.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b><u>For cohort and cross-sectional studies:</u></b> There is indirect evidence (i.e., stated by the authors without providing a description) that groups were not similar (as described above for the high confidence rating). <b>AND</b></li> <li>Control for differences in exposure groups is not adequately controlled for in the statistical analysis.</li> <li><b><u>For case-control studies:</u></b> There is indirect evidence (i.e., stated by the authors without providing a description) that cases and controls were not similar (as described above for the high confidence rating). <b>AND</b></li> </ul>

Confidence Level (Score)	Description
	<ul style="list-style-type: none"> <li>The characteristics of cases and controls are not reported (Source: [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;re type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook fo assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;ye Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;ur urls&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;E date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Control for differences in the case and control groups is not adequately controlled for in the statistical analysis.</li> <li><b><i>For studies reporting SMRs or SIRs:</i></b> Indirect evidence of a lack of adjustment or stratification for age or sex choice of reference population (e.g., general population) is appropriate.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b><i>For cohort studies:</i></b> Subjects in all exposure groups were not similar</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Information was not reported to determine if participants in all exposure groups were similar [STROBE Check &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Von Elm&lt;/Author&gt;&lt;Year&gt;2008&lt;/Year&gt;&lt;RecNum&gt;111126&lt;/RecNum&gt;&lt;IDText&gt;Elm et al., 2008&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111126&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521205718"&gt;111126&lt;/key&gt;&lt;/foreign-keys&gt;&lt;re type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Von Elm, E.&lt;/author&gt;&lt;author&gt;Altman, D. G.&lt;/author&gt;&lt;author&gt;Egge J.&lt;/author&gt;&lt;author&gt;Götzsche, P. C.&lt;/author&gt;&lt;author&gt;Vandenbroucke, J. P.&lt;/author&gt;&lt;/authors&gt;&lt;/contributo Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observatio title&gt;Journal of Clinical Epidemiology&lt;/secondary-title&gt;&lt;alt-title&gt;J Clin Epidemiol&lt;/alt-title&gt;&lt;short-title&gt;Jo title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-p 349&lt;/pages&gt;&lt;volume&gt;61&lt;/volume&gt;&lt;number&gt;4&lt;/number&gt;&lt;dates&gt;&lt;year&gt;2008&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 0 4356&lt;/isbn&gt;&lt;label&gt;4263036&lt;/label&gt;&lt;urls&gt;&lt;related- urls&gt;&lt;url&gt;https://hero.epa.gov/heronet/index.cfm/reference/download/reference_id/4263036&lt;/url&gt;&lt;/related-u &lt;/custom1&gt;&lt;electronic-resource-num&gt;10.1016/j.jclinepi.2007.11.008&lt;/electronic-resource-num&gt;&lt;/record&gt;&lt;/</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Potential differences in exposure groups were not controlled for in the statistical analysis.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Subjects in the exposure groups had very different participation/response rates [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;re type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook fo assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;ye Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;ur urls&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;E date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul> <p><b><i>For case-control studies:</i></b> Controls were drawn from a very dissimilar population than cases or recruited with EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;re type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook fo assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;ye Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;ur</p>

Confidence Level (Score)	Description
	<p>urls&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;E date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</p> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Potential differences in the case and control groups were not controlled for in the statistical analysis.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Rationale and/or methods for case and control selection, matching criteria including number of controls per case [STROBE Checklist 6 [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Von Elm&lt;/Author&gt;&lt;Year&gt;2008&lt;/Year&gt;&lt;RecNum&gt;111126&lt;/RecNum&gt;&lt;IDText&gt;4263036&lt;/IDText&gt;&lt;DisplayText&gt;2008)&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111126&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521205718"&gt;111126&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Elm, E.&lt;/author&gt;&lt;author&gt;Altman, D. G.&lt;/author&gt;&lt;author&gt;Egger, M.&lt;/author&gt;&lt;author&gt; Pocock, S. J.&lt;/author&gt;&lt;author&gt;C.&lt;/author&gt;&lt;author&gt;Vandenbroucke, J. P.&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies&lt;/title&gt;&lt;secondary-title&gt;Epidemiology&lt;/secondary-title&gt;&lt;alt-title&gt;J Clin Epidemiol&lt;/alt-title&gt;&lt;short-title&gt;Journal of Clinical Epidemiology&lt;/short-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-349&lt;/pages&gt;&lt;volume&gt;61&lt;/volume&gt;&lt;number&gt;4&lt;/number&gt;&lt;dates&gt;&lt;year&gt;2008&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 1473-3099&lt;/isbn&gt;&lt;label&gt;4263036&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;https://hero.epa.gov/heronet/index.cfm/reference/download/reference_id/4263036&lt;/url&gt;&lt;/related-urls&gt;&lt;/custom1&gt;&lt;electronic-resource-num&gt;10.1016/j.jclinepi.2007.11.008&lt;/electronic-resource-num&gt;&lt;/record&gt;&lt;/EndNote&gt;].</li> <li>• <b><u>For cross-sectional studies:</u></b> Subjects in all exposure groups were not similar, recruited within very different participation/response rates [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a)&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for conducting health hazard assessments using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;U.S. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;urls&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;E date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Potential differences in exposure groups were not controlled for in the statistical analysis.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Sources and methods of selection of participants in all exposure groups were not reported [STROBE Checklist 4 [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Von Elm&lt;/Author&gt;&lt;Year&gt;2008&lt;/Year&gt;&lt;RecNum&gt;111126&lt;/RecNum&gt;&lt;IDText&gt;4263036&lt;/IDText&gt;&lt;DisplayText&gt;2008)&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111126&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521205718"&gt;111126&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Von Elm, E.&lt;/author&gt;&lt;author&gt;Altman, D. G.&lt;/author&gt;&lt;author&gt;Egger, M.&lt;/author&gt;&lt;author&gt; Pocock, S. J.&lt;/author&gt;&lt;author&gt;Götzsche, P. C.&lt;/author&gt;&lt;author&gt;Vandenbroucke, J. P.&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies&lt;/title&gt;&lt;secondary-title&gt;Journal of Clinical Epidemiology&lt;/secondary-title&gt;&lt;alt-title&gt;J Clin Epidemiol&lt;/alt-title&gt;&lt;short-title&gt;Journal of Clinical Epidemiology&lt;/short-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-349&lt;/pages&gt;&lt;volume&gt;61&lt;/volume&gt;&lt;number&gt;4&lt;/number&gt;&lt;dates&gt;&lt;year&gt;2008&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 1473-3099&lt;/isbn&gt;&lt;label&gt;4263036&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;https://hero.epa.gov/heronet/index.cfm/reference/download/reference_id/4263036&lt;/url&gt;&lt;/related-urls&gt;&lt;/custom1&gt;&lt;electronic-resource-num&gt;10.1016/j.jclinepi.2007.11.008&lt;/electronic-resource-num&gt;&lt;/record&gt;&lt;/EndNote&gt;].</li> <li>• <b><u>For studies reporting SMRs or SIRs:</u></b> Lack of adjustment or stratification for both age and sex (if applicable) in the general population) is not reported.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>

Confidence Level (Score)	Description
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]</i>
<b>Domain 2. Exposure Characterization</b>	
<b>Metric 4. Measurement of Exposure (Detection/measurement/information, performance biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> Exposure was consistently assessed (i.e., using the same method and sampling time-frame) personal and/or industrial hygiene data used to determine levels of exposure, a frequently used biomarker of exposure (e.g., measurement of the chemical in the environment (air, drinking water, consumer product, etc.) or measurement of biological matrix such as blood, plasma, urine, etc.) (NTP, 2015a).</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>For an occupational population, contains detailed employment records which allows for construction of a job-exposure matrix (i.e., cumulative or peak exposures, and time since first exposure).</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> Exposure was directly measured and assessed using a method that is not well-established (e.g., exposure), <i>but</i> is validated against a well-established method and demonstrated a high agreement between the two methods.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>For an occupational study population, contains detailed employment records for only a portion of participant's work history (e.g., later years), such that extrapolation of the missing years is required.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> A less-established method (e.g., newly developed biomarker of exposure) was used and not validated against well-established methods, but there was little to no evidence that the method had poor validity and little to no misclassification (e.g., differential recall of self-reported exposure) (Source: OHAT).</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>For an occupational study population, exposure was estimated solely using professional judgement.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> Methods used to quantify the exposure were not well defined, and sources of data and data collection were not reported [STROBE Checklist 7 and 8]</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Exposure was assessed using methods known or suspected to have poor validity (Source: OHAT).</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>There is evidence of substantial exposure misclassification that would significantly bias the results.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]</i>
<b>Metric 5. Exposure levels (Detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> The range and distribution of exposure is sufficient or adequate to develop an exposure-response model (e.g., 3121908).</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Reports 3 or more levels of exposure (referent group + 2 or more) or an exposure-response model using a continuous exposure metric.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> The range of exposure in the population is limited</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Reports 2 levels of exposure (e.g., exposed/unexposed) (Cooper) (Source: IRIS).</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b><i>For all study types:</i></b> The range and distribution of exposure are not adequate to determine an exposure-response model</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Exposure levels are not reported in a way that allows for construction of an exposure-response model</li> </ul>



Confidence Level (Score)	Description
	<p>6750&lt;/isbn&gt;&lt;accession-num&gt;HERO ID: 3121908&lt;/accession-num&gt;&lt;label&gt;3121908&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;http://dx.doi.org/10.1016/j.envint.2016.03.017&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;electronic-resource-num&gt;10.1016/j.envint.2016.03.017&lt;/electronic-resource-num&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/C&gt;</p> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• No description is provided on the levels or range of exposure.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]</i>
<b>Metric 6. Temporality (Detection/measurement/information biases)</b>	
High (score = 1)	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> The study presents an appropriate temporality between exposure and outcome (i.e. the exposure precedes the outcome).</li> <li>• The interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration (Lakind et al., 2014).</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> Temporality is established, but it is unclear whether exposures fall within relevant exposure windows (Lakind et al., 2014).</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> The temporality of exposure and outcome is uncertain</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> Study lacks an established time order, such that exposure is not likely to have occurred prior to the outcome.           <p>&lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Lakind&lt;/Author&gt;&lt;Year&gt;2014&lt;/Year&gt;&lt;RecNum&gt;111083&lt;/RecNum&gt;&lt;IDText&gt;111083&lt;/IDText&gt;&lt;DisplayText&gt;et al., 2014)&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111083&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrrwa" timestamp="1521049323"&gt;111083&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type&gt;Journal Article&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Lakind, J. S.&lt;/author&gt;&lt;author&gt;Sobus, J.&lt;/author&gt;&lt;author&gt;Goodman, B.&lt;/author&gt;&lt;author&gt;Fuerst, P.&lt;/author&gt;&lt;author&gt;Albertini, R. J.&lt;/author&gt;&lt;author&gt;Arbuckle, T.&lt;/author&gt;&lt;author&gt;Auer, G.&lt;/author&gt;&lt;author&gt;Tan, Y.&lt;/author&gt;&lt;author&gt;Teeguarden, J.&lt;/author&gt;&lt;author&gt;Tornero-Velez, R.&lt;/author&gt;&lt;author&gt;Tost, P.&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;A proposal for assessing study quality: Biomonitoring, Environmental Health Chemicals (BEES-C) instrument&lt;/title&gt;&lt;secondary-title&gt;Environment International&lt;/secondary-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Environment International&lt;/full-title&gt;&lt;abbr-1&gt;Environ Int&lt;/abbr-1&gt;&lt;/alt-periodical&gt;&lt;pages&gt;195-207&lt;/pages&gt;&lt;volume&gt;73&lt;/volume&gt;&lt;dates&gt;&lt;year&gt;2014&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 0160-4120&lt;/isbn&gt;&lt;electronic-resource-num&gt;25137624&lt;/accession-num&gt;&lt;label&gt;2713602&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;http://dx.doi.org/10.1016/j.envint.2014.07.011&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;electronic-resource-num&gt;10.1016/j.envint.2014.07.011&lt;/electronic-resource-num&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/C&gt;</p> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• There was inadequate follow-up of the cohort for the expected latency period.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Sources of data and details of methods of assessment were not sufficiently reported (e.g. duration of follow-up, ascertainment, etc.) Source: STROBE Checklist 8 [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Von Elm&lt;/Author&gt;&lt;Year&gt;2008&lt;/Year&gt;&lt;RecNum&gt;111126&lt;/RecNum&gt;&lt;IDText&gt;4263036&lt;/IDText&gt;&lt;DisplayText&gt;2008)&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111126&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrrwa" timestamp="1521205718"&gt;111126&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;Elm, E.&lt;/author&gt;&lt;author&gt;Altman, D. G.&lt;/author&gt;&lt;author&gt;Egger, M.&lt;/author&gt;&lt;author&gt;Pocock, S. J.&lt;/author&gt;&lt;author&gt;Vandenbroucke, J. P.&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies&lt;/title&gt;&lt;secondary-title&gt;Epidemiology&lt;/secondary-title&gt;&lt;alt-title&gt;J Clin Epidemiol&lt;/alt-title&gt;&lt;short-title&gt;Journal of Clinical Epidemiology&lt;/short-title&gt;&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-periodical&gt;&lt;pages&gt;349&lt;/pages&gt;&lt;volume&gt;61&lt;/volume&gt;&lt;number&gt;4&lt;/number&gt;&lt;dates&gt;&lt;year&gt;2008&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 0950-2688&lt;/isbn&gt;&lt;electronic-resource-num&gt;4356&lt;/accession-num&gt;&lt;label&gt;4263036&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;https://hero.epa.gov/heronet/index.cfm/reference/download/reference_id/4263036&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;electronic-resource-num&gt;10.1016/j.jclinepi.2007.11.008&lt;/electronic-resource-num&gt;&lt;/record&gt;&lt;/C&gt;</li> </ul> </li> </ul>
Not	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>

Confidence Level (Score)	Description
rated/applicable	
Reviewer's comments	[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]
<b>Domain 3. Outcome Assessment</b>	
<b>Metric 7. Outcome measurement or characterization (detection/measurement/information, performance, reporting biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li><b>For cohort studies:</b> The outcome was assessed using well-established methods (e.g., the “gold standard”).</li> <li><b>For case-control studies:</b> The outcome was assessed in cases (i.e., case definition) and controls using well-established methods. Subjects had been followed for the same length of time in all study groups (NTP, 2015a).</li> <li><b>For cross-sectional studies:</b> There is direct evidence that the outcome was assessed using well-established methods.</li> </ul> <p><b>*Note:</b> Acceptable assessment methods will depend on the outcome, but examples of such methods may include: laboratory diagnostic methods, measured by trained interviewers, obtained from registries (NTP, 2015a; Shamliyan et al., 2015).</p>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b>For all study types:</b> A less-established method was used and no method validation was conducted against well-established methods to no evidence that the method had poor validity and little to no evidence of outcome misclassification (e.g., exposure status).</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b>For cohort studies:</b> The outcome assessment method is an insensitive instrument or measure.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>The length of follow up differed by study group (NTP, 2015a).</li> <li><b>For case-control studies:</b> The outcome was assessed in cases (i.e., case definition) using an insensitive instrument or measure.</li> <li><b>For cross-sectional studies:</b> The outcome assessment method is an insensitive instrument or measure (NTP, 2015a).</li> <li>Any self-reported information</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b>For all study types:</b> Diagnostic criteria were not defined or reported [STROBE Checklist 15 (Von Elm et al., 2007)].</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Do not select for this metric</li> </ul>
Reviewer's comments	[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]
<b>Metric 8. Reporting Bias</b>	
High (score = 1)	<ul style="list-style-type: none"> <li><b>For all study types:</b> A description of measured outcomes is reported in the methods, abstract, and/or introduction, including confidence interval and/or standard errors; number of cases/controls or exposed/unexposed reported for each outcome; and response analysis or fully tabulated during data extraction and analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;U.S. Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b>For all study types:</b> All of the study's measured outcomes (primary and secondary) outlined in the methods, and relevant for the evaluation) are reported, but not in a way that would allow for detailed extraction (e.g., results, tables, or accompanying data were not shown).</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b>For all study types:</b> All of the study's measured outcomes (primary and secondary) outlined in the methods, and relevant for the evaluation) have not been reported.</li> </ul> <p><b>*Note:</b> In addition to not reporting outcomes, this would include reporting outcomes based on composite scores, summary components or outcomes reported using measurements, analysis methods, or unplanned analyses were included (NTP, 2015a).</p>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>

Confidence Level (Score)	Description
rated/applicable	
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]</i>
Domain 4. Potential Confounding/Variable Control	
Metric 9. Covariate Adjustment (confounding)	
High (score = 1)	<ul style="list-style-type: none"> <li><b>For all study types:</b> Appropriate adjustments or explicit considerations were made for potential confounders exposures, which are evaluated in metric 11) in the final analyses through the use of statistical models to reduce matching, adjustment in multivariate models, stratification, or other methods that were appropriately justified [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> <li><b>For Studies reporting SMRs or SIRs:</b> Adjustments are described and results are age-, race-, and sex-adjusted (or stratified) if applicable (i.e., confounding was demonstrated and was not appropriately adjusted for in the final analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b>For all study types:</b> There is indirect evidence that appropriate adjustments were made (i.e., considerations without providing a description of methods).</li> <li><b>OR</b></li> <li>The distribution of potential confounders (excluding co-exposures) did not differ significantly between exposure groups.</li> <li><b>OR</b></li> <li>The major potential confounders (excluding co-exposures) were appropriately adjusted (e.g., SMRs, SIRs, etc.) and not to appreciably bias the results</li> <li><b>For Studies reporting SMRs or SIRs:</b> Indirect evidence that results are age- and sex-adjusted (or stratified) if applicable (i.e., confounding was demonstrated and was not appropriately adjusted for in the final analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b>For all study types:</b> There is indirect evidence (i.e., no description is provided in the study) that consideration of potential confounders adjustment in the final analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> <li><b>AND</b></li> <li>The distribution of primary covariates (excluding co-exposures) and potential confounders was not reported between cases and controls [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> <li><b>For Studies reporting SMRs or SIRs:</b> Results are age-, race-, OR sex-adjusted (or stratified) if applicable (i.e., confounding was demonstrated and was not appropriately adjusted for in the final analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b>For all study types:</b> The distribution of potential confounders differed significantly between the exposure groups.</li> <li><b>AND</b></li> <li>Confounding was demonstrated and was not appropriately adjusted for in the final analyses [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;NTP&lt;/Author&gt;&lt;Year&gt;2015&lt;/Year&gt;&lt;RecNum&gt;111085&lt;/RecNum&gt;&lt;IDText&gt;282015a&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</li> </ul>

Confidence Level (Score)	Description
	<p>2015a)&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111085&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="t2a0z5v5utrzw3er9abxvzfvtwd99tfvrwwa" timestamp="1521049493"&gt;111085&lt;/key&gt;&lt;/foreign-keys&gt;&lt;record-type&gt;&lt;contributors&gt;&lt;authors&gt;&lt;author&gt;NTP,&lt;/author&gt;&lt;/authors&gt;&lt;/contributors&gt;&lt;titles&gt;&lt;title&gt;Handbook for assessment using OHAT approach for systematic review and evidence integration&lt;/title&gt;&lt;/titles&gt;&lt;dates&gt;&lt;year&gt;2015&lt;/year&gt;&lt;/dates&gt;&lt;publisher&gt;Dept. of Health and Human Services, National Toxicology Program&lt;/publisher&gt;&lt;label&gt;2823411&lt;/label&gt;&lt;url&gt;&lt;url&gt;http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html&lt;/url&gt;&lt;/related-urls&gt;&lt;/urls&gt;&lt;language&gt;English&lt;/language&gt;&lt;date&gt;National Toxicology Program&lt;/modified-date&gt;&lt;/record&gt;&lt;/Cite&gt;&lt;/EndNote&gt;].</p> <ul style="list-style-type: none"> <li>• <b><u>For Studies reporting SMRs or SIRs:</u></b> No discussion of adjustments. Results are not adjusted for both age and sex.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 10. Covariate Characterization (measurement/information, confounding biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> Potential confounders (excluding co-exposures; e.g. age, sex, SES, etc.) were assessed using appropriate (e.g., validated questionnaires, biomarker).</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> A less-established method was used to assess confounders (excluding co-exposures) and compared against well-established methods, but there was little to no evidence that that the method had poor validity and reliability.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> The confounder (excluding co-exposures) assessment method is an insensitive instrument with poor validity.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> Confounders were assessed using a method or instrument known to be invalid.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> Covariates were not assessed.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 11. Co-exposure Confounding (measurement/information, confounding biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> Any co-exposures to pollutants that are not the target exposure that would likely bias the results were appropriately measured or either directly or indirectly adjusted for.</li> <li>OR</li> <li>• Co-exposures to pollutants were appropriately measured or either directly or indirectly adjusted for.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>• <b><u>For cohort and cross-sectional studies:</u></b> There is direct evidence that there was an unbalanced provision of additional co-exposures to pollutants in study groups, which were not appropriately adjusted for.</li> <li>• <b><u>For case-control studies:</u></b> There is direct evidence that there was an unbalanced provision of additional co-exposures to pollutants in study groups, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>• Enter 'NA' and do not score this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Domain 5. Analysis</b>	
<b>Metric 12. Study Design and Methods</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>• Do not select for this metric.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>• <b><u>For all study types:</u></b> The study design chosen was appropriate for the research question (e.g. assess the association between common chronic diseases over time with cohort studies, assess the association between exposure and risk of disease with a cross-sectional study design, assess the association between exposure levels and acute disease with a cross-sectional study design).</li> <li>AND</li> <li>• The study uses an appropriate statistical method to address the research question(s) (e.g., repeated measures ANOVA, logistic regression analysis for case-control studies, or mean, median, etc. for descriptive studies)</li> </ul>

Confidence Level (Score)	Description
Low (score = 3)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> The study design chosen was not appropriate for the research question.</li> <li><b>OR</b></li> <li>Inappropriate statistical analyses were applied to assess the research questions.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]</i>
<b>Metric 13. Statistical power (sensitivity)</b>	
High (score = 1)	Do not select for this metric.
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><u>For cohort and cross-sectional studies:</u></b> The number of participants are adequate to detect an effect in the exposed total population.</li> <li><b>OR</b></li> <li>The paper reported statistical power is high enough (<math>\geq 80\%</math>) to detect an effect in the exposure population and</li> <li><b><u>For case-control studies:</u></b> The number of cases and controls are adequate to detect an effect in the exposed population.</li> <li><b>OR</b></li> <li>The paper reported statistical power is high enough (<math>\geq 80\%</math>) to detect an effect in the exposure population and</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li><b><u>For cohort and cross-sectional studies:</u></b> The number of participants is inadequate to detect an effect in the exposed total population</li> <li><b><u>For case-control studies:</u></b> The number of cases and controls is inadequate to detect an effect in the exposed population</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight such as relevance]</i>
<b>Metric 14. Reproducibility of analyses [adapted from [ HYPERLINK "https://hero.epa.gov/index.cfm?action=search&amp;term="]</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> The description of the analysis is sufficient to understand precisely what has been done and access to the analytic data.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> The description of the analysis is insufficient to understand what has been done and to b analyses are not present (e.g., statistical tests and estimation procedures were not described, variables used in transformations of continuous variables (e.g., logarithmic) were not explained, rules for categorization of conf exclusion of outliers was not elucidated and how missing values are dealt with was not mentioned).</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 15. Statistical Models (confounding bias)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li><b><u>For all study types:</u></b> The model or method for calculating the risk estimates (e.g., odds ratios, SMRs, SIR) variables were included or excluded).</li> <li><b>AND</b></li> </ul>

Confidence Level (Score)	Description
	<ul style="list-style-type: none"> <li>Model assumptions were met.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li><b>For all study types:</b> The statistical model building process is not fully appropriate <b>OR</b> model assumptions were not present (STROBE Checklist 12e [ ADDIN EN.CITE &lt;EndNote&gt;&lt;Cite&gt;&lt;Author&gt;Von Elm&lt;/Author&gt;&lt;Year&gt;2008&lt;/Year&gt;&lt;RecNum&gt;111126&lt;/RecNum&gt;&lt;IDText&gt;4263036&lt;/IDText&gt;&lt;DisplayText&gt;2008&lt;/DisplayText&gt;&lt;record&gt;&lt;rec-number&gt;111126&lt;/rec-number&gt;&lt;foreign-keys&gt;&lt;key app="EN" db-id="12" timestamp="1521205718"&gt;111126&lt;/key&gt;&lt;/foreign-keys&gt;&lt;ref-type name="Journal Article"&gt;17&lt;/ref-type&gt;&lt;author&gt;Elm, E.&lt;/author&gt;&lt;author&gt;Altman, D. G.&lt;/author&gt;&lt;author&gt;Egger, M.&lt;/author&gt;&lt;author&gt;Pocock, S. J.&lt;/author&gt;&lt;author&gt;C.&lt;/author&gt;&lt;author&gt;Vandenbroucke, J. P.&lt;/author&gt;&lt;/authors&gt;&lt;contributors&gt;&lt;title&gt;&lt;title&gt;The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies&lt;/title&gt;&lt;secondary-title&gt;&lt;secondary-title&gt;J Clin Epidemiol&lt;/alt-title&gt;&lt;short-title&gt;Journal of Clinical Epidemiology&lt;/titles&gt;&lt;periodical&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-title&gt;&lt;full-title&gt;Journal of Clinical Epidemiology&lt;/full-title&gt;&lt;abbr-1&gt;J Clin Epidemiol&lt;/abbr-1&gt;&lt;/alt-title&gt;&lt;/pages&gt;&lt;volume&gt;61&lt;/volume&gt;&lt;number&gt;4&lt;/number&gt;&lt;dates&gt;&lt;year&gt;2008&lt;/year&gt;&lt;/dates&gt;&lt;isbn&gt;ISSN 0950-2688&lt;/isbn&gt;&lt;label&gt;4263036&lt;/label&gt;&lt;urls&gt;&lt;related-urls&gt;&lt;url&gt;https://hero.epa.gov/heronet/index.cfm/reference/download/reference_id/4263036&lt;/url&gt;&lt;/related-urls&gt;&lt;/custom1&gt;&lt;electronic-resource-num&gt;10.1016/j.jclinepi.2007.11.008&lt;/electronic-resource-num&gt;&lt;/record&gt;&lt;/li&gt;</li></ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' if the study did not use a statistical model.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Domain 6. Other (if applicable) Considerations for Biomarker Selection and Measurement</b>	
<b>Metric 16. Use of Biomarker of Exposure (detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, and/or effect.</li> <li><b>AND</b></li> <li>Biomarker is derived from exposure to one parent chemical.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, and/or effect.</li> <li><b>AND</b></li> <li>Biomarker is derived from multiple parent chemicals.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose, and/or effect, but the method of assessment of accuracy and precision or none was reported.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Biomarker in a specified matrix is a poor surrogate (low accuracy, specificity, and precision) for exposure/dose/effect.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric if no biomarker of exposure was measured.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 17. Effect biomarker (detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Effect biomarker measured is an indicator of a key event in an AOP.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>Biomarkers of effect shown to have a relationship to health outcomes using well validated methods, but the method is not well validated and/or the biomarker is not specific to a health outcome.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>Biomarkers of effect shown to have a relationship to health outcomes, but the method is not well validated and/or the biomarker is not specific to a health outcome.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Biomarker has undetermined consequences (e.g., biomarker is not specific to a health outcome).</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric if no biomarker of effect was measured.</li> </ul>
Reviewer's comments	
<b>Metric 18. Method sensitivity (detection/measurement/information biases)</b>	

Confidence Level (Score)	Description
High (score = 1)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research hypothesis. LOD/LOQ (value or %) are reported.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>Frequency of detection too low to address the research hypothesis.</li> </ul> <p><b>OR</b></p> <p>LOD/LOQ (value or %) are not stated</p>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight strengths or elements such as relevance]</i>
<b>Metric 19. Biomarker stability (detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Samples with a known storage history and documented stability data or those using real-time measurements.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>Samples have known losses during storage, but the difference between low and high exposures can be quantified.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of degradation.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric if no biomarkers were assessed.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight strengths or elements such as relevance]</i>
<b>Metric 20. Sample contamination (detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Samples are contamination-free from the time of collection to the time of measurement (e.g., by use of certified reference materials, and appropriate use of blanks both in the field and lab).</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Documentation of the steps taken to provide the necessary assurance that the study data are reliable is included.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>Samples are stated to be contamination-free from the time of collection to the time of measurement.</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable.</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>Samples are known to have contamination issues, but steps have been taken to address and correct contamination.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Samples are stated to be contamination-free from the time of collection to the time of measurement, but there is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable.</li> </ul>
Unacceptable (4)	<ul style="list-style-type: none"> <li>There are known contamination issues and no documentation that the issues were addressed.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric if no samples were collected.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight strengths or elements such as relevance]</i>
<b>Metric 21. Method requirements (detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (e.g., LC-MS/MS).</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required quantitation.</li> </ul>
Low	<ul style="list-style-type: none"> <li>Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferences.</li> </ul>

Confidence Level (Score)	Description
(score = 3)	
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric if biomarkers were not measured.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>
<b>Metric 22. Matrix adjustment (detection/measurement/information biases)</b>	
High (score = 1)	<ul style="list-style-type: none"> <li>If applicable for the biomarker under consideration, study provides results, either in the main publication or as unadjusted matrix concentrations (e.g., creatinine-adjusted or specific gravity-adjusted and non-adjusted urine) for adjustment approach.</li> </ul>
Medium (score = 2)	<ul style="list-style-type: none"> <li>If applicable for the biomarker under consideration, study only provides results using one method (matrix-adjusted).</li> </ul>
Low (score = 3)	<ul style="list-style-type: none"> <li>If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.</li> </ul>
Unacceptable (score = 4)	<ul style="list-style-type: none"> <li>Do not select for this metric.</li> </ul>
Not rated/applicable	<ul style="list-style-type: none"> <li>Enter 'NA' and do not score the metric if not applicable for the biomarker or no biomarker was assessed.</li> </ul>
Reviewer's comments	<i>[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight elements such as relevance]</i>

## Overall Judgement Guidance

The confidence levels and corresponding scores at the metric level are defined as follows:

- High:** No notable deficiencies or concerns are identified in the domain metric that are likely to influence results [score of 1].
- Medium:** Minor uncertainties or limitations are noted in the domain metric that are unlikely to have a substantial impact on results [score of 2].
- Low:** Deficiencies or concerns are noted in the domain metric that are likely to have a substantial impact on results [score of 3].
- Unacceptable:** Serious flaws are noted in the domain metric that consequently make the data/information source unusable. [score of 4].
- Not rated/applicable:** Rating of this metric is not applicable to the data/information source being evaluated [no score]. *Not rated/applicable* will also be used in cases in which studies cite a literature source for their test methodology instead of providing detailed descriptions. In these circumstances, the metric is scored as *not rated/not applicable* and the reason is captured in the evaluator's notes. If the data/information source is not classified as "unacceptable" in the initial review, the cited literature source will be reviewed during a subsequent evaluation step and the metric will be rated at that time.

## References

[ ADDIN EN.REFLIST ]